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10/551,901	10/04/2005	Hiroshi Miura	277987US0PCT	6206

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EXAMINER	
PALENIK, JEFFREY T	
ART UNIT	**PAPER NUMBER**
1615	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/551,901	MIURA ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *14-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of Applicants' Amendments and Remarks filed 18 July 2008. The Examiner acknowledges the following:

Claims 1-13 have been amended. Where support for the amendments was not expressly provided, it was found either within Applicants' disclosure and/or originally filed claims. The Examiner acknowledges that no new matter has been added to the claims.

Claims 14-23 which were previously only withdrawn from consideration currently remain so.

No claims have been cancelled and no further claims have been added.

Thus, claims 1-13 still represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statement (IDS) have been submitted for consideration.

WITHDRAWN OBJECTIONS/REJECTIONS

Objection to the Specification

Applicants' amendments to both the Abstract and Title of the Invention renders moot their objection. Thus, said objections have been **withdrawn**.

Objection to the Claims

Applicants' amendments to claims 8-13, correcting improper dependencies limitations, render moot the objections to claims 8-13. Thus, said objections have been **withdrawn**.

Rejection under 35 USC 112

Applicants' amendments removing the phrase, "solid solution" from claim 1, and clarifying the language regarding the second drug in claim 2, render moot the rejections to claims 1 and 2, under 35 USC 112, second paragraph. Thus, said rejections have been **withdrawn**.

Rejection under 35 USC 102(b)

Applicants' amendments to the instant claims, namely claim 1, renders moot the rejection to claims 1-13 under 35 USC 102(b) as being anticipated by Ohkuchi et al. (USPN 6,348,468). Thus, said rejection has been **withdrawn**.

Applicants' amendments to the instant claims, namely claim 1, renders moot the rejection to claims 1-13 under 35 USC 102(b) as being anticipated by Yamamoto et al. (USPN 5,236,906). Thus, said rejection has been **withdrawn**.

Rejection under 35 USC 103(a)

Applicants' amendments to the instant claims, namely claim 1, render moot the rejection to claims 1-11 and 13 under 35 USC 103(a) as being unpatentable over the machine translation of Nakanishi et al. (JP 2002-345940) in view of Koishi et al. (JP 61-227520). Thus, said rejection has been **withdrawn**.

Applicants' amendments to the instant claims, namely claim 1, render moot the rejection to claims 1-13 under 35 USC 103(a) as being unpatentable over Ohkuchi et al. in view of Sigma-Aldrich Silica Gel Product N° 403653. Thus, said rejection has been **withdrawn**.

Rejection under Nonstatutory Obviousness-Type Double-Patenting

Applicants' amendments to both the instant claim 1 and copending claim 21 of Application number 10/554,921 differentiate the instantly claimed porous materials used in the respective applications. The instant claim 1 has been amended such that it specifically excludes using porous silica material having the claimed properties of the porous silica material of the copending application. That said, the instant claims still do include porous silica material within the recited claims [emphasis added]. However, the difference is that the silica materials of the instant invention fall outside of the scope of the silica materials recited in the copending '921 application, as defined by Applicants' instant disclosure (see pg. 9, line 10 to pg. 10, line 1). Thus, said rejection has been **withdrawn**.

NEW REJECTIONS

In light of Applicants' amendments, most notably to claim 1, the following rejections have been newly added:

SPECIFICATION

The amendment filed 18 July 2008 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall

introduce new matter into the disclosure of the invention. The change in material which is not supported by the original disclosure is as follows: **removal** of Examples 7 and 8, as well as Comparative Examples 3 and 4 from Table 1 (page 22 of either Specification) and associated text thereto (pp. 18-21; Spec. filed 4 Oct. 2005). Applicant has also amended the disclosure **adding** the following sections: (1) Production Example 2, and (2) Industrial Applicability. The Examiner expressly notes that the changes made to Applicants' instant disclosure, either in the form of additions or removals, without providing any corresponding discussion constitutes unsupported **new matter**.

Applicant is required to cancel the new matter in the reply to this Office Action.

CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Verhoff et al. (US Pre-Grant Publication N° 2002/0047058).

The instantly amended claims are now directed to a composition comprising a very low water-soluble drug and a porous material, wherein said drug has a solubility of less than 10 μg/mL at 25°C prior to treatment and said porous material is not a porous silica material having the recited properties (claim 1 and 5-10). The limitation whereby said composition is "produced by treating a mixture … with a supercritical or subcritical carbon dioxide fluid" is still

interpreted by the Examiner as a product-by-process limitation which holds no patentable weight (MPEP §2113), particularly in absence of evidence to the criticality of the limitation. With regard to the limitations recited in claim 1, which states that said drug "has a solubility of less than 10 μg/mL at 25°C prior to treatment"; until some material difference in the properties of the composition are demonstrated, said limitation is considered by the Examiner to be directed toward "a very low water-soluble drug" (i.e. a water-insoluble or poorly-soluble drug), which is instantly claimed. The porous material, as discussed above, is further limited to recited embodiments which fall outside of the scope of the porous silica material parameters excluded in claim 1. Limitations to the porous material, such as silicon dioxide, are further recited (claims 2-4). With regard to the limitations recited in claims 5-10, which state limitations to the porous material such as "wherein the porous material has an average pore diameter of…" or "wherein the porous material has a specific surface area of …"; until some material differences in the properties of the porous material of the composition or in the composition itself are demonstrated, said limitations are considered by the Examiner to be directed towards the instantly claimed composition. Claim 13 recites a drug composition comprising the composition of the instant claim 1 (i.e. a composition comprising a poorly soluble drug and a porous material).

Verhoff et al. teach the preparation of a drug product (e.g. composition) comprising a commixture small particles of a solid substrate and small particles of a first material, the combination of which is treated (e.g. milled) in the presence of a fluid carrier (claim 1). Said solid substrate is further taught as either a poorly water-soluble or water-insoluble pharmaceutical agent (claims 5 and 6). The small particles of first material are further taught as

consisting of silicon dioxide (claim 17). Verhoff expressly teaches using drugs which are insoluble in water. The term "insoluble" is interpreted by the Examiner as teaching zero solubility in water, which is less than the recited property limitation of the instantly claimed drug. Regarding the exclusionary properties of the silica material recited in the instant claim 1, as well as the parameters of claims 2 and 3, the teaching of silicon dioxide in claim 17 as the "first material" expressly anticipates these properties. Furthermore, the "fluid carrier" of claim 1, is further taught in ¶[0149] as comprising a single component or mixture or solution of one or more subcritical or supercritical fluid such as supercritical carbon dioxide. Given these teachings, it further follows that the drug product of the instant claim 13 is also clearly anticipated.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verhoff et al. (US Pre-Grant Publication N° 2002/0047058) in view of Yanaki et al. (USPN 5,538,728).

The instantly amended claims are directed to a composition comprising a very low water-soluble drug and a porous material and a drug product thereto, as discussed above. Claim 11 further limits the composition by reciting a weight ratio of the drug to the porous material ranging from 0.1:1 to 1:1,000. Claim 12 recites that the drug is either 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyradazin-3-one or prednisolone valerate acetate.

The teachings of Verhoff et al. are discussed above. Verhoff further teaches that the poorly-soluble/water-insoluble active agent may comprise drug classes such as anti-inflammatory agents and steroid hormonal agents such as prednisolone and prednisone ¶[0256] and [0257]. Preferred milling media compositions are taught as comprising adjustable concentrations of the solid substrate, fluid carrier and milling media bodies of a first material depending upon the application ¶[0247]. For example, the ratio of the first material (e.g. silicon dioxide) to a second material is taught as ranging as broadly from 1:1000 to 1000:1.

Verhoff fails to expressly teach Applicants' claimed ratio range of drug to porous material, recited in claim 11, as well as either of Applicants' claimed drug species, recited in claim 12. However, it is known in the art that compositions comprising porous silicate materials such as silicon dioxide may be prepared further complexing with it poorly soluble active pharmaceutical agents are taught as evidenced by Yanaki et al.

Yanaki et al. teach a pharmaceutical composition comprising a complexation of a water-swellable silicate mineral and a drug (claims 12 and 1). Said water-swellable silicate material is taught as including silicon dioxide (col. 4, lines 15-20). The pharmaceutical used in the invention while not particularly limited, is generally taught as including a steroid hormone such as prednisolone valerate acetate, for instance where the application applies to rectal administration (col. 10, lines 40-45).

Similar to Verhoff, Yanaki fails to expressly teach Applicants' claimed drug/porous material ratio ranging as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a composition comprising the combination of a poorly water-soluble drug and a porous silica material as taught by Verhoff and suggested by the combination of Verhoff and Yanaki, modify the ratio of drug to porous material, and produce the instantly claimed composition.

One of ordinary skill in the art would have been motivated to do this because Verhoff expressly teaches the instantly claimed porous silicon dioxide/drug composition, including

preparing said composition by milling in the presence of a fluid carrier such as supercritical carbon dioxide. Though Verhoff does not expressly teach incorporating prednisolone valerate acetate as the poorly water-soluble active ingredient complexed in the preparation, the motivation to do so is provided by the fact that Verhoff does teach using the less-derivatized steroidal anti-inflammatory prednisolone as the insoluble solid substrate ¶[0257]. Coupled with the guidance of the invention to Yanaki, the skilled artisan would be well motivated to substitute prednisolone valerate acetate for prednisolone in the invention to Verhoff and produce the instant invention.

The combined references do not expressly teach the ratio limitations of poorly-soluble drug to porous material, as instantly claimed by Applicants. Since the values of each parameter with respect to the claimed composition are adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. In the instant case, the skilled artisan, would be highly motivated to adjust the aforementioned ratio in view of the teachings presented by Verhoff where it is discussed that the concentrations of the components in the preparation (i.e. the first material, the solid substrate and the milling media) can be optimized based on such requirements as milling performance and flow characteristics of the substrate to be milled ¶[0247]. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

All claims have been rejected; no claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966.

The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615